CASE REPORTS

Cessation of *Cryptosporidium*-Associated Diarrhea in an Acquired Immunodeficiency Syndrome Patient After Treatment With Hyperimmune Bovine Colostrum

BETH L. P. UNGAR, DOUGLAS J. WARD, RONALD FAYER, and CAROLE A. QUINN

Division of Tropical Public Health, Uniformed Services University of the Health Sciences, Bethesda, Maryland; George Washington University Hospital, Washington, D.C.; and the Zoonotic Diseases Laboratory, United States Department of Agriculture, Beltsville, Maryland

Cryptosporidium is a parasite of the human gastrointestinal tract that can cause life-threatening diarrhea in immunodeficient patients. Although more than 80 agents have been tried with occasional anecdotal success, treatment remains primarily limited to hydration. A 38-yr-old homosexual man with antibody to human immunodeficiency virus and *Cryptosporidium*-related diarrhea is described. The patient excreted 6–12 L of stool per day for at least 3 mo, 2 of them spent in the hospital. Trials with more th 6 antidiarrheal medications were ineffective. T patient received bovine colostrum hyperimmune to *Cryptosporidium* by direct duodenal infusion. During infusion, the patient's fecal output decreased to less than 2 L per day, and 48 h after treatment, stools were formed and oocysts to *Cryptosporidium* were absent. The patient remained asymptomatic for 3 mo. Hyperimmune bovine colostrum offers an exciting new therapy for cryptosporidiosis; controlled trials to establish efficacy should be undertaken and the active factor(s) characterized.

Cryptosporidium is now well recognized as a cause of diarrhea worldwide (1,2). In both immunologically healthy and deficient individuals, it can cause profound symptoms that may wax and wane but rarely last more than 30 days in immunologically competent persons and remit in immunosuppressed hosts only when the cause of immunosuppression is removed. In acquired immunodeficiency syndrome (AIDS) patients, *Cryptosporidium* infections generally persist for life and may be associated with life-threatening diarrhea. In 1986, an estimated 3.6% of AIDS patients in the United States had cryptosporidiosis (3), and *Cryptosporidium* was identified in 15% of patients with AIDS and diarrhea evaluated at the National Institutes of Health (4) and 16% of those evaluated at the Johns Hopkins Hospital (5).

Treatment of infected individuals has been limited to oral or intravenous hydration, because more than 80 chemotherapeutic, biologic, and other antidiarrheal agents have not been found efficacious (2). Orally administered spiramycin, a macrolide antibiotic, may produce improvement in some patients, although clinical trials have not been promising (6–9). A long-acting parenterally administered somatostatin analogue, octreotide acetate, may also have occasional utility (10,11). Attention has recently focused on use of bovine-derived products because of the high frequency of cryptosporidiosis in cattle (12,13). In 1 study, 3 patients with cryptosporidiosis were not helped by orally administered bovine colostrum from cows previously naturally infected with *Cryptosporidium* (13). However, other studies using specially produced hyperimmune bovine colostrum in 3 patients (including 1 with AIDS) with cryptosporidiosis in Australia (14,15), and

Abbreviations used in this paper: AIDS, acquired immunodeficiency syndrome; AZT, azidothymidine.

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in a calf animal model (16), suggest that such colostrum may have therapeutic and/or protective efficacy. We report the cessation of fulminant diarrhea and *Cryptosporidium* oocyst shedding in an AIDS patient for 3 mo after treatment with bovine colostrum specifically hyperimmune to *Cryptosporidium*.

Case Report

The patient was a 38-yr-old homosexual man in previously good health. His medical history was significant only for a cholecystectomy for gallstones at 8 yr of age. In August 1988, approximately 1 mo before this hospitalization, the patient developed profuse watery diarrhea with up to 20 bowel movements per day associated with abdominal cramping. Stools did not contain blood or mucus. He was treated as an outpatient with tetracycline and antimotility agents without effect. Subsequently, on fecal examination, *Cryptosporidium* was identified, without other significant parasitic or bacterial pathogens, including *Clostridium difficile* and *Mycobacterium avium-intracellulare*. The patient was found to have serum antibody to human immunodeficiency virus by enzyme-linked immunosorbent assay and Western blot, with a CD4 count of 106 cells per mm^3 (helper/suppressor ratio 0.04). Metronidazole, additional antimotility agents, and hydration were also given when he was an outpatient, but voluminous diarrhea persisted, and the patient was admitted to the hospital for intravenous hydration in September 1988.

On admission the patient was weak, complaining of intermittent abdominal cramping and nausea, with occasional vomiting. Results of his physical examination were remarkable only for signs of moderate dehydration, results of his abdominal examination were benign. He had a blood urea nitrogen concentration of 63 mg/dl, creatinine concentration of 1.9 mg/dl, and potassium concentration of 1.4 mg/dl. Other laboratory results, including albumin, amylase, and liver function tests, were within normal limits. Fluid and electrolyte deficits were replaced, and maintenance intravenous fluids and hyperalimentation were given; however, stool output of 6–12 L/day persisted. The hospital course was complicated by toxic megacolon requiring surgical decompression and placement of a cecostomy tube, disseminated herpes zoster, and subclavian vein thrombosis related to central lines, all of which responded to appropriate therapy. His diarrhea showed no response to bismuth subsalicylate, H_2-histamine antagonists, nonsteroidal anti-inflammatory agents, or azidothymidine (AZT) (Burroughs Wellcome Co., Research Triangle Park, N.C.). A 3-wk course of oral spiramycin (3 g/day) was ineffective. Results of stool examinations after modified acid-fast staining continued to be markedly positive for *Cryptosporidium* (5.2 oocysts per oil-immersion microscopic field, averaged from examination of 10 fields), with no other pathogens identified by standard microbiologic techniques. Specific immunoglobulin G (IgG) antibodies to *Cryptosporidium* were markedly elevated in the patient's serum by enzyme-linked immunosorbent assay (17). An intestinal biopsy sample was unobtainable.

After 2 mo of hospitalization, 1 mo on AZT, and approximately 10 days after completion of spiramycin therapy, the patient was treated with hyperimmune bovine colostrum given via a nasoduodenal tube at a continuous flow of 20 cm^3/h. Informed consent was obtained from the patient after the experimental nature of the therapy had been explained. Two infusions were initially given over a 24-h period, but treatment was then disrupted when the tube dislodged. Fecal examination during this period showed an average of 0.5 oocysts per oil-immersion field. Treatment was restarted 7 days later and continued uninterrupted for 60 h. Within 24 h of reinstitution of therapy, fecal volume had decreased to less than 2 L/day (Figure 1). Shortly thereafter, no oocysts could be identified in stool specimens. Within 48 h of cessation of therapy, stools were fully formed, and oocysts of *Cryptosporidium* could not be found in fecal specimens in 2 different laboratories by microscopic examination after specimen concentration in Sheather's sucrose solution and modified acid-fast staining. Intravenous fluids were discontinued, and the patient was discharged 1 wk later on a normal diet. In the 3 mo after treatment, the patient remained diarrhea- and oocyst-free. Subsequently, diarrhea and cryptosporidiosis did recur, but retreatment was not possible.

The hyperimmune bovine colostrum was prepared as previously described (10) by parenteral injection and intramammary infusion of *Cryptosporidium* oocysts into pregnant dairy cows. Colostrum was collected immediately after parturition before calves could nurse. Specific antibodies to *Cryptosporidium* in the colostrum were assayed by enzyme-linked immunosorbent assay (17). Titers were at least 1:200,000 for the specific bovine IgG-1, IgA, and IgM antibodies. The colostrum was stored at −70°C and was exposed to a sterilizing dose of 29.6 kGy using linear accelerator A' (Armed Forces Radiobiology Research Institute, Bethesda, Md.) before administration while still frozen. It was thawed immediately before use.

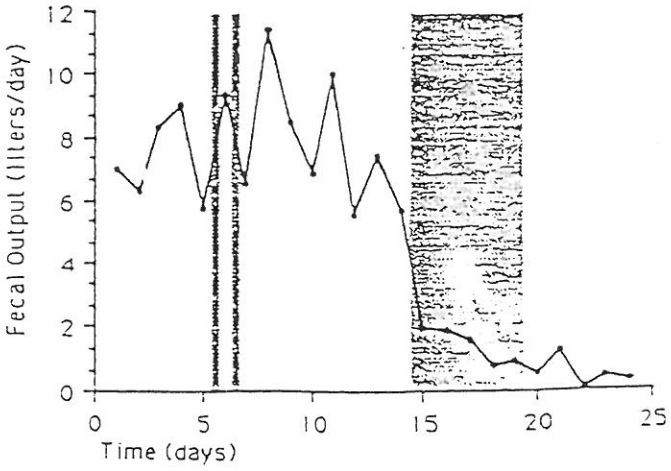

Figure 1. Fecal output in an AIDS patient with fulminant cryptosporidiosis before, during, and after treatment with hyperimmune bovine colostrum. Shaded areas represent periods of colostrum administration. No other antidiarrheals were given during the time period graphed.

Discussion

The present case represents the first time hyperimmune bovine colostrum has been used successfully to achieve both remission of symptoms and elimination of *Cryptosporidium* oocysts detectable by fecal examination in an adult AIDS patient. Three Australian patients given a 10–21-day course of specific hyperimmune bovine colostrum became diarrhea free within 3–5 days, but only 1, a child with leukemia on immunosuppressive therapy, remained parasite free (14,15). Although it is possible that concomitant AZT contributed to the present patient's dramatic response, the colostrum most likely was responsible for his remission. The presence of an elevated concentration of specific anti-*Cryptosporidium* IgG in his serum indicates that this antibody is not sufficient to control infection. Absence of the gallbladder may be significant, that 1 Australian patient treated with hyperimmune bovine colostrum apparently had his intestinal *Cryptosporidium* eliminated but had persistent organisms in his gall bladder (15).

The active ingredient(s) in the hyperimmune bovine colostrum is (are) unknown. Bovine IgG-1 is most analogous to human IgA and may have a protective role similar to that postulated for bovine IgG-1 in enterotoxigenic *Escherichia coli*–related diarrhea (18). However, it is equally possible that the biologically important agent in colostrum is a cytokine or other as-yet-unidentified product, and that the increased levels of detectable antibody simply reflect a hyperimmunized state. Potential mechanisms of action that might explain an early clinical response to therapy and decrease in detectable oocysts seen in the patient reported here include (1) blocking of intestinal receptor sites with interruption of the extracellular autoinfective life cycle stages, or (2) providing a critical substance absent because of diminished CD4 cells that activates other intact portions of the immune network. The rapid clinical response of all patients with cryptosporidiosis treated with hyperimmune colostrum is noteworthy (14,15).

Cryptosporidium infection is important not only in AIDS patients but also in immunocompetent persons. Worldwide, based on fecal examinations for *Cryptosporidium* oocysts, generally between 2% and 4% of persons in more-developed areas and 8%–10% of persons in less-developed areas of the world excrete oocysts (1). Groups particularly at risk include travelers to endemic areas, animal handlers (farmers, laboratory workers), and contacts of infected individuals (household and sexual contacts; health-care and day-care workers); water-borne outbreaks affecting as many as 13,000 persons have also been reported (19). Controlled trials to establish the efficacy of hyperimmune bovine colostrum (particularly feasible as adequate volumes of appropriately prepared colostrum become available and with potential direct biliary-tract infusion) and characterization of the active factor(s) in hyperimmune bovine colostrum will be important in developing better prophylaxis and therapy for cryptosporidiosis for all.

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